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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: ANDERSON, John P.	Examiner: Malgorzata A. Walicka
Application No.: 09/471,669	Art Unit: 1652
Filed: December 24, 1999	PETITION TO WITHDRAW APPLICATION FROM ISSUANCE PURSUANT TO 37 C.F.R. §1.313(c)(2)
For: BETA-SECRETASE ENZYME COMPOSITIONS AND METHODS	

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Sir:

Applicants request withdrawal of the application from issuance pursuant to 37 CFR 1.313(c)(2). Applicants also attach a Request for Continuing Examination (RCE) in the event that this petition is granted. A Supplemental Information Disclosure Statement for consideration in the RCE is attached.

Please charge the fee of $130 to Deposit Account No. 20-1430. Please charge any other fees or credit any overpayments to the same account. If the Examiner believes a telephone

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conference would expedite prosecution of this application, please telephone the undersigned at (650) 326-2400.

Respectfully submitted,

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Please stamp the date of receipt of the enclosed documents and return this card to addressee:

1. Request for Continued Examination (RCE) Transmittal (1 page);
2. Fee Transmittal (1 page, submitted in duplicate);
3. Amendment (34 pages)
4. Supplemental Information Disclosure Statement Under 37 CFR §1.97 and §1.98;
5. PTO/SB08A (1 page);
6. Copies of cited references 113-138;
7. Petition to Withdraw Application From Issuance Pursuant to 37 CFR §1.313(c)(2)(2 pgs); and,
8. Return Postcard.

File No. 015270-006430US R. Celli /A. Baker

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PATENT
Attorney Docket No.: 015270-006430US
Client Ref. No.: 228-US-NEW

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

John P. Anderson et al.

Application No.: 09/471,669

Filed: December 24, 1999

For: BETA-SECRETASE ENZYME COMPOSITIONS AND METHODS

Customer No.: 20350

Confirmation No.

Examiner: Walicka, Malgorzata A.

Technology Center/Art Unit: 1652

AMENDMENT

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Sir:

This paper is being submitted with a Petition to Withdraw Application From Issuance Pursuant to 37 C.F.R § 1.313(c)(2), an Request for Continued Examination, a Supplemental Information Disclosure with attached PTO/SB/08A form, and references (cite nos. 113-138. Please enter the following amendments and remarks:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 32 of this paper.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings of claims in the application:

Listing of Claims:

1-47. (Withdrawn)

48. (Currently Amended) An isolated nucleic acid, comprising a sequence of nucleotides that encodes SEQ ID NO: 43~~, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO:69,~~ or a complementary sequence of any of such nucleotides.

49-50. (Canceled)

51. (Currently Amended) An expression vector, comprising the isolated nucleic acid of claim 48 and a promoter, wherein the nucleic acid and the promoter are operably linked~~; and operably linked to said nucleic acid, regulatory sequences effective for expression of the nucleic acid in a selected host cell~~.

52. (Original) The recombinant expression vector of claim 51, wherein said vector is suitable for transfection of a bacterial cell.

53. (Original) A heterologous cell transfected with the vector of claim 51, wherein said cell expresses a biologically active β-secretase.

54. (Original) The cell of claim 53, wherein said cell is a eukaryotic cell.

55. (Original) The cell of claim 53, wherein said cell is a bacterial cell.

56. (Original) The cell of claim 53, wherein said cell is an insect cell.

57. (Original) The cell of claim 53, wherein said cell is a yeast cell.

58. (Currently Amended) A method of producing a recombinant β-secretase enzyme, comprising culturing a cell transfected with a vector comprising a sequence of

nucleotides that encodes ~~SEQ ID NO: 2,~~ SEQ ID NO: 43~~, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 74, SEQ ID NO: 75, a β-secretase protein,~~ or a complementary sequence of such nucleotides under conditions to promote growth of said cell, and subjecting an extract or cultured medium from said cell to an affinity matrix.

59. (Original) The method of claim 58, wherein said affinity matrix contains a β-secretase inhibitor molecule.

60. (Previously Amended) The method of claim 59, wherein said inhibitor molecule is P10-P4'staD->V (SEQ ID NO:73).

61. (Original) The method of claim 58, wherein said matrix contains an antibody characterized by an ability to bind β-secretase.

62. (Currently Amended) The method of claim 61, wherein said antibody binds specifically to ~~any of the protein compositions of SEQ ID NO: 2,~~ SEQ ID NO: 43~~, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 74, SEQ ID NO: 75, or a β secretase protein~~.

63. (Previously Amended) The method of claim 61, wherein said antibody further lacks significant immunoreactivity with a protein having the sequence of SEQ ID NO: 2.

64. (Currently Amended) A heterologous cell, comprising

(i) a nucleic acid molecule encoding SEQ ID NO: 43~~, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 69,~~ or the complementary sequence of said nucleic acid molecule;

(ii) a nucleic acid molecule encoding a β-secretase substrate molecule; and

(iii) operatively linked to (i) and (ii), a regulatory sequence effective for expression of said nucleic acid molecules in said cell.

65. (Original)) The cell of claim 64, wherein said nucleic acid encoding said β-secretase protein is heterologous to said cell.

66. (Previously Amended) The cell of claim 64, wherein both said nucleic acids encoding said β-secretase protein and encoding said β-secretase substrate molecule are heterologous to said cell.

67. (Original) The cell of claim 64, wherein said β-secretase substrate molecule is selected from the group consisting of APPwt, APPsw, and β-secretase cleavable fragments thereof.

68. (Previously Amended) The cell of claim 64, wherein said β-secretase substrate is selected from the group consisting of a maltose binding protein fused at the carboxy-terminus to the 125 carboxyl-terminal amino acids of APP having the cleavage site of SEQ ID NO: 54 (MBP-C125wt) and a maltose binding protein fused at the carboxy-terminus to the 125 C-terminus amino acids of APP having the cleavage site of SEQ ID NO: 51 (MBP-C125sw).

69. (Currently Amended) The cell of claim 67, wherein said β-secretase-cleavable fragment is ~~selected from the group consisting of~~ SEQ ID NO: 82~~; SEQ ID NO: 83; SEQ ID NO: 84; SEQ ID NO: 85; SEQ ID NO: 86; SEQ ID NO: 87; SEQ ID NO: 88; SEQ ID NO: 89; SEQ ID NO: 90; SEQ ID NO: 91; SEQ ID NO: 92; SEQ ID NO: 93; SEQ ID NO: 94; SEQ ID NO: 95; and SEQ ID NO: 96~~.

70-113. (Canceled)

114. (New) An isolated nucleic acid, comprising a sequence of nucleotides that encodes SEQ ID NO: 58 or a complementary sequence of any of such nucleotides.

115. (New) An expression vector, comprising the isolated nucleic acid of claim 114 and a promoter, wherein the nucleic acid and the promoter are operably linked.

116. (New) The expression vector of claim 115, wherein said vector is suitable for transfection of a bacterial cell.

117. (New) A heterologous cell transfected with the vector of claim 115, wherein said cell expresses a biologically active β-secretase.

118. (New) The cell of claim 117, wherein said cell is a eukaryotic cell.

119. (New) The cell of claim 117, wherein said cell is a bacterial cell.

120. (New) The cell of claim 117, wherein said cell is an insect cell.

121. (New) The cell of claim 117, wherein said cell is a yeast cell.

122. (New) An isolated nucleic acid, comprising a sequence of nucleotides that encodes SEQ ID NO: 59 or a complementary sequence of any of such nucleotides.

123. (New) An expression vector, comprising the isolated nucleic acid of claim 122 and a promoter, wherein the nucleic acid and the promoter are operably linked.

124. (New) The expression vector of claim 123, wherein said vector is suitable for transfection of a bacterial cell.

126. (New) A heterologous cell transfected with the vector of claim 123, wherein said cell expresses a biologically active β-secretase.

127. (New) The cell of claim 126, wherein said cell is a eukaryotic cell.

128. (New) The cell of claim 126, wherein said cell is a bacterial cell.

129. (New) The cell of claim 126, wherein said cell is an insect cell.

130. (New) The cell of claim 126, wherein said cell is a yeast cell.

131. (New) An isolated nucleic acid, comprising a sequence of nucleotides that encodes SEQ ID NO: 66 or a complementary sequence of any of such nucleotides.

132. (New) An expression vector, comprising the isolated nucleic acid of claim 131 and a promoter, wherein the nucleic acid and the promoter are operably linked.

133. (New) The expression vector of claim 132, wherein said vector is suitable for transfection of a bacterial cell.

134. (New) A heterologous cell transfected with the vector of claim 132, wherein said cell expresses a biologically active β-secretase.

135. (New) The cell of claim 134, wherein said cell is a eukaryotic cell.

136. (New) The cell of claim 134, wherein said cell is a bacterial cell.

137. (New) The cell of claim 134, wherein said cell is an insect cell.

138. (New) The cell of claim 134, wherein said cell is a yeast cell.

139. (New) An isolated nucleic acid, comprising a sequence of nucleotides that encodes SEQ ID NO: 67 or a complementary sequence of any of such nucleotides.

140. (New) An expression vector, comprising the isolated nucleic acid of claim 139 and a promoter, wherein the nucleic acid and the promoter are operably linked.

141. (New) The expression vector of claim 140, wherein said vector is suitable for transfection of a bacterial cell.

142. (New) A heterologous cell transfected with the vector of claim 140, wherein said cell expresses a biologically active β-secretase.

143. (New) The cell of claim 142, wherein said cell is a eukaryotic cell.

144. (New) The cell of claim 142, wherein said cell is a bacterial cell.

145. (New) The cell of claim 142, wherein said cell is an insect cell.

146. (New) The cell of claim 142, wherein said cell is a yeast cell.

147. (New) An isolated nucleic acid, comprising a sequence of nucleotides that encodes SEQ ID NO: 68 or a complementary sequence of any of such nucleotides.

148. (New) An expression vector, comprising the isolated nucleic acid of claim 147 and a promoter, wherein the nucleic acid and the promoter are operably linked.

149. (New) The expression vector of claim 148, wherein said vector is suitable for transfection of a bacterial cell.

150. (New) A heterologous cell transfected with the vector of claim 148, wherein said cell expresses a biologically active β-secretase.

151. (New) The cell of claim 150, wherein said cell is a eukaryotic cell.

152. (New) The cell of claim 150, wherein said cell is a bacterial cell.

153. (New) The cell of claim 150, wherein said cell is an insect cell.

154. (New) The cell of claim 150, wherein said cell is a yeast cell.

155. (New) An isolated nucleic acid, comprising a sequence of nucleotides that encodes SEQ ID NO: 69 or a complementary sequence of any of such nucleotides.

156. (New) An expression vector, comprising the isolated nucleic acid of claim 155 and a promoter, wherein the nucleic acid and the promoter are operably linked.

157. (New) The expression vector of claim 156, wherein said vector is suitable for transfection of a bacterial cell.

158. (New) A heterologous cell transfected with the vector of claim 156, wherein said cell expresses a biologically active β-secretase.

159. (New) The cell of claim 158, wherein said cell is a eukaryotic cell.

160. (New) The cell of claim 158, wherein said cell is a bacterial cell.

161. (New) The cell of claim 158, wherein said cell is an insect cell.

162. (New) The cell of claim 158, wherein said cell is a yeast cell.

163. (New) An isolated nucleic acid, comprising a sequence of nucleotides that encodes SEQ ID NO: 70 or a complementary sequence of any of such nucleotides.

164. (New) An expression vector, comprising the isolated nucleic acid of claim 163 and a promoter, wherein the nucleic acid and the promoter are operably linked.

165. (New) The expression vector of claim 163, wherein said vector is suitable for transfection of a bacterial cell.

166. (New) A heterologous cell transfected with the vector of claim 164, wherein said cell expresses a biologically active β-secretase.

167. (New) The cell of claim 166, wherein said cell is a eukaryotic cell.

168. (New) The cell of claim 166, wherein said cell is a bacterial cell.

169. (New) The cell of claim 166, wherein said cell is an insect cell.

170. (New) The cell of claim 166, wherein said cell is a yeast cell.

171. (New) An isolated nucleic acid, comprising a sequence of nucleotides that encodes SEQ ID NO: 74 or a complementary sequence of any of such nucleotides

172. (New) An expression vector, comprising the isolated nucleic acid of claim 171 and a promoter, wherein the nucleic acid and the promoter are operably linked.

173. (New) The expression vector of claim 172, wherein said vector is suitable for transfection of a bacterial cell.

174. (New) A heterologous cell transfected with the vector of claim 172, wherein said cell expresses a biologically active β-secretase.

175. (New) The cell of claim 174, wherein said cell is a eukaryotic cell.

176. (New) The cell of claim 174, wherein said cell is a bacterial cell.

177. (New) The cell of claim 174, wherein said cell is an insect cell.

178. (New) The cell of claim 174, wherein said cell is a yeast cell.

179. (New) A method of producing a recombinant β-secretase enzyme, comprising culturing a cell transfected with a vector comprising a sequence of nucleotides that encodes SEQ ID NO: 58 or a complementary sequence of such nucleotides under conditions to promote growth of said cell, and subjecting an extract or cultured medium from said cell to an affinity matrix.

180. (New) The method of claim 179, wherein said affinity matrix contains a β-secretase inhibitor molecule.

181. (Previously Amended) The method of claim 180, wherein said inhibitor molecule is P10-P4'staD->V (SEQ ID NO:73).

182. (New) The method of claim 179, wherein said matrix contains an antibody characterized by an ability to bind β-secretase.

183. (New) The method of claim 182, wherein said antibody binds specifically to SEQ ID NO: 58.

184. (New) The method of claim 182, wherein said antibody further lacks significant immunoreactivity with a protein having the sequence of SEQ ID NO: 2.

185. (New) A method of producing a recombinant β-secretase enzyme, comprising culturing a cell transfected with a vector comprising a sequence of nucleotides that encodes SEQ ID NO: 59 or a complementary sequence of such nucleotides under conditions to promote growth of said cell, and subjecting an extract or cultured medium from said cell to an affinity matrix.

186. (New) The method of claim 185, wherein said affinity matrix contains a β-secretase inhibitor molecule.

187. (New) The method of claim 186, wherein said inhibitor molecule is P10-P4'staD->V (SEQ ID NO:73).

188. (New) The method of claim 185, wherein said matrix contains an antibody characterized by an ability to bind β-secretase.

189. (New) The method of claim 188, wherein said antibody binds specifically to SEQ ID NO: 59.

190. (New) The method of claim 188, wherein said antibody further lacks significant immunoreactivity with a protein having the sequence of SEQ ID NO: 2.

191. (New) A method of producing a recombinant β-secretase enzyme, comprising culturing a cell transfected with a vector comprising a sequence of nucleotides that encodes SEQ ID NO: 66 or a complementary sequence of such nucleotides under conditions to promote growth of said cell, and subjecting an extract or cultured medium from said cell to an affinity matrix.

192. (New) The method of claim 191, wherein said affinity matrix contains a β-secretase inhibitor molecule.

193. (New) The method of claim 192, wherein said inhibitor molecule is P10-P4'staD->V (SEQ ID NO:73).

194. (New) The method of claim 191, wherein said matrix contains an antibody characterized by an ability to bind β-secretase.

195. (New) The method of claim 194, wherein said antibody binds specifically to SEQ ID NO: 66.

196. (New) The method of claim 194, wherein said antibody further lacks significant immunoreactivity with a protein having the sequence of SEQ ID NO: 2.

197. (New) A method of producing a recombinant β-secretase enzyme, comprising culturing a cell transfected with a vector comprising a sequence of nucleotides that encodes SEQ ID NO: 67 or a complementary sequence of such nucleotides under conditions to promote growth of said cell, and subjecting an extract or cultured medium from said cell to an affinity matrix.

198. (New) The method of claim 197, wherein said affinity matrix contains a β-secretase inhibitor molecule.

199. (New) The method of claim 198, wherein said inhibitor molecule is P10-P4'staD->V (SEQ ID NO:73).

200. (New) The method of claim 197, wherein said matrix contains an antibody characterized by an ability to bind β-secretase.

201. (New) The method of claim 200, wherein said antibody binds specifically to SEQ ID NO: 67.

202. (New) The method of claim 197, wherein said antibody further lacks significant immunoreactivity with a protein having the sequence of SEQ ID NO: 2.

203. (New) A method of producing a recombinant β-secretase enzyme, comprising culturing a cell transfected with a vector comprising a sequence of nucleotides that encodes SEQ ID NO: 68 or a complementary sequence of such nucleotides under conditions to promote growth of said cell, and subjecting an extract or cultured medium from said cell to an affinity matrix.

204. (New) The method of claim 203, wherein said affinity matrix contains a β-secretase inhibitor molecule.

205. (New) The method of claim 204, wherein said inhibitor molecule is P10-P4'staD->V (SEQ ID NO:73).

206. (New) The method of claim 203, wherein said matrix contains an antibody characterized by an ability to bind β-secretase.

207. (New) The method of claim 206, wherein said antibody binds specifically to SEQ ID NO: 68.

208. (New) The method of claim 206, wherein said antibody further lacks significant immunoreactivity with a protein having the sequence of SEQ ID NO: 2.

209. (New) A method of producing a recombinant β-secretase enzyme, comprising culturing a cell transfected with a vector comprising a sequence of nucleotides that encodes SEQ ID NO: 69 or a complementary sequence of such nucleotides under conditions to promote growth of said cell, and subjecting an extract or cultured medium from said cell to an affinity matrix.

210. (New) The method of claim 209, wherein said affinity matrix contains a β-secretase inhibitor molecule.

211. (New) The method of claim 210, wherein said inhibitor molecule is P10-P4'staD->V (SEQ ID NO:73).

212. (New) The method of claim 211, wherein said matrix contains an antibody characterized by an ability to bind β-secretase.

213. (New) The method of claim 209, wherein said antibody binds specifically to SEQ ID NO: 69.

214. (New) The method of claim 212, wherein said antibody further lacks significant immunoreactivity with a protein having the sequence of SEQ ID NO: 2.

215. (New) A method of producing a recombinant β-secretase enzyme, comprising culturing a cell transfected with a vector comprising a sequence of nucleotides that encodes SEQ ID NO: 70 or a complementary sequence of such nucleotides under conditions to promote growth of said cell, and subjecting an extract or cultured medium from said cell to an affinity matrix.

216. (New) The method of claim 215, wherein said affinity matrix contains a β-secretase inhibitor molecule.

217. (New) The method of claim 216, wherein said inhibitor molecule is P10-P4'staD->V (SEQ ID NO:73).

218. (New) The method of claim 215, wherein said matrix contains an antibody characterized by an ability to bind β-secretase.

219. (New) The method of claim 218, wherein said antibody binds specifically to SEQ ID NO: 70.

220. (New) The method of claim 218, wherein said antibody further lacks significant immunoreactivity with a protein having the sequence of SEQ ID NO: 2.

221. (New) A method of producing a recombinant β-secretase enzyme, comprising culturing a cell transfected with a vector comprising a sequence of nucleotides that encodes SEQ ID NO: 74 or a complementary sequence of such nucleotides under conditions to promote growth of said cell, and subjecting an extract or cultured medium from said cell to an affinity matrix.

222. (New) The method of claim 221, wherein said affinity matrix contains a β-secretase inhibitor molecule.

223. (New) The method of claim 222, wherein said inhibitor molecule is P10-P4'staD->V (SEQ ID NO:73).

224. (New) The method of claim 221, wherein said matrix contains an antibody characterized by an ability to bind β-secretase.

225. (New) The method of claim 224, wherein said antibody binds specifically to SEQ ID NO: 74.

226. (New) The method of claim 221, wherein said antibody further lacks significant immunoreactivity with a protein having the sequence of SEQ ID NO: 2.

227. (New) The cell of claim 67, wherein said β-secretase-cleavable fragment is SEQ ID NO: 83.

228. (New) The cell of claim 67, wherein said β-secretase-cleavable fragment is SEQ ID NO: 84.

229. (New) The cell of claim 67, wherein said β-secretase-cleavable fragment is SEQ ID NO: 85.

230. (New) The cell of claim 67, wherein said β-secretase-cleavable fragment is SEQ ID NO: 86.

231. (New) The cell of claim 67, wherein said β-secretase-cleavable fragment is SEQ ID NO: 87.

232. (New) The cell of claim 67, wherein said β-secretase-cleavable fragment is SEQ ID NO: 88.

233. (New) The cell of claim 67, wherein said β-secretase-cleavable fragment is SEQ ID NO: 89.

234. (New) The cell of claim 67, wherein said β-secretase-cleavable fragment is SEQ ID NO: 90.

235. (New) The cell of claim 67, wherein said β-secretase-cleavable fragment is SEQ ID NO: 91.

236. (New) The cell of claim 67, wherein said β-secretase-cleavable fragment is SEQ ID NO: 92.

237. (New) The cell of claim 67, wherein said β-secretase-cleavable fragment is SEQ ID NO: 93.

238. (New) The cell of claim 67, wherein said β-secretase-cleavable fragment is SEQ ID NO: 94.

239. (New) The cell of claim 67, wherein said β-secretase-cleavable fragment is SEQ ID NO: 95.

240. (New) The cell of claim 67, wherein said β-secretase-cleavable fragment is SEQ ID NO: 96.

241. (New) A heterologous cell, comprising

(i) a nucleic acid molecule encoding SEQ ID NO: 58 or the complementary sequence of said nucleic acid molecule;

(ii) a nucleic acid molecule encoding a β-secretase substrate molecule; and

(iii) operatively linked to (i) and (ii), a regulatory sequence effective for expression of said nucleic acid molecules in said cell.

242. (New) The cell of claim 241, wherein said nucleic acid encoding said β-secretase protein is heterologous to said cell.

243. (New) The cell of claim 241, wherein both said nucleic acids encoding said β-secretase protein and encoding said β-secretase substrate molecule are heterologous to said cell.

244. (New) The cell of claim 241, wherein said β-secretase substrate molecule is selected from the group consisting of APPwt, APPsw, and β-secretase cleavable fragments thereof.

245. (New) The cell of claim 241, wherein said β-secretase substrate is selected from the group consisting of a maltose binding protein fused at the carboxy-terminus to the 125 carboxyl-terminal amino acids of APP having the cleavage site of SEQ ID NO: 54 (MBP-C125wt) and a maltose binding protein fused at the carboxy-terminus to the 125 C-terminus amino acids of APP having the cleavage site of SEQ ID NO: 51 (MBP-C125sw).

246. (New) The cell of claim 244, wherein said β-secretase-cleavable fragment is SEQ ID NO: 83.

247. (New) The cell of claim 244, wherein said β-secretase-cleavable fragment is SEQ ID NO: 84.

248. (New) The cell of claim 244, wherein said β-secretase-cleavable fragment is SEQ ID NO: 85.

249. (New) The cell of claim 244, wherein said β-secretase-cleavable fragment is SEQ ID NO: 86.

250. (New) The cell of claim 244, wherein said β-secretase-cleavable fragment is SEQ ID NO: 87.

251. (New) The cell of claim 244, wherein said β-secretase-cleavable fragment is SEQ ID NO: 88.

252. (New) The cell of claim 244, wherein said β-secretase-cleavable fragment is SEQ ID NO: 89.

253. (New) The cell of claim 244, wherein said β-secretase-cleavable fragment is SEQ ID NO: 90.

254. (New) The cell of claim 244, wherein said β-secretase-cleavable fragment is SEQ ID NO: 91.

255. (New) The cell of claim 244, wherein said β-secretase-cleavable fragment is SEQ ID NO: 92.

256. (New) The cell of claim 244, wherein said β-secretase-cleavable fragment is SEQ ID NO: 93.

257. (New) The cell of claim 244, wherein said β-secretase-cleavable fragment is SEQ ID NO: 94.

258. (New) The cell of claim 244, wherein said β-secretase-cleavable fragment is SEQ ID NO: 95.

259. (New) The cell of claim 244, wherein said β-secretase-cleavable fragment is SEQ ID NO: 96.

260. (New) A heterologous cell, comprising

(i) a nucleic acid molecule encoding SEQ ID NO: 59 or the complementary sequence of said nucleic acid molecule;

(ii) a nucleic acid molecule encoding a β-secretase substrate molecule; and

(iii) operatively linked to (i) and (ii), a regulatory sequence effective for expression of said nucleic acid molecules in said cell.

261. (New) The cell of claim 260, wherein said nucleic acid encoding said β-secretase protein is heterologous to said cell.

262. (New) The cell of claim 260, wherein both said nucleic acids encoding said β-secretase protein and encoding said β-secretase substrate molecule are heterologous to said cell.

263. (New) The cell of claim 260, wherein said β-secretase substrate molecule is selected from the group consisting of APPwt, APPsw, and β-secretase cleavable fragments thereof.

264. (New) The cell of claim 260, wherein said β-secretase substrate is selected from the group consisting of a maltose binding protein fused at the carboxy-terminus to the 125 carboxyl-terminal amino acids of APP having the cleavage site of SEQ ID NO: 54 (MBP-C125wt) and a maltose binding protein fused at the carboxy-terminus to the 125 C-terminus amino acids of APP having the cleavage site of SEQ ID NO: 51 (MBP-C125sw).

265. (New) The cell of claim 263, wherein said β-secretase-cleavable fragment is SEQ ID NO: 83.

266. (New) The cell of claim 263, wherein said β-secretase-cleavable fragment is SEQ ID NO: 84.

267. (New) The cell of claim 263, wherein said β-secretase-cleavable fragment is SEQ ID NO: 85.

268. (New) The cell of claim 263, wherein said β-secretase-cleavable fragment is SEQ ID NO: 86.

269. (New) The cell of claim 263, wherein said β-secretase-cleavable fragment is SEQ ID NO: 87.

270. (New) The cell of claim 263, wherein said β-secretase-cleavable fragment is SEQ ID NO: 88.

271. (New) The cell of claim 263, wherein said β-secretase-cleavable fragment is SEQ ID NO: 89.

272. (New) The cell of claim 263, wherein said β-secretase-cleavable fragment is SEQ ID NO: 90.

273. (New) The cell of claim 263, wherein said β-secretase-cleavable fragment is SEQ ID NO: 91.

274. (New) The cell of claim 263, wherein said β-secretase-cleavable fragment is SEQ ID NO: 92.

275. (New) The cell of claim 263, wherein said β-secretase-cleavable fragment is SEQ ID NO: 93.

276. (New) The cell of claim 263, wherein said β-secretase-cleavable fragment is SEQ ID NO: 94.

277. (New) The cell of claim 263, wherein said β-secretase-cleavable fragment is SEQ ID NO: 95.

278. (New) The cell of claim 263, wherein said β-secretase-cleavable fragment is SEQ ID NO: 96.

279. (New) A heterologous cell, comprising

(i) a nucleic acid molecule encoding SEQ ID NO: 66 or the complementary sequence of said nucleic acid molecule;

(ii) a nucleic acid molecule encoding a β-secretase substrate molecule; and

(iii) operatively linked to (i) and (ii), a regulatory sequence effective for expression of said nucleic acid molecules in said cell.

280. (New) The cell of claim 279, wherein said nucleic acid encoding said β-secretase protein is heterologous to said cell.

281. (New) The cell of claim 279, wherein both said nucleic acids encoding said β-secretase protein and encoding said β-secretase substrate molecule are heterologous to said cell.

282. (New) The cell of claim 279, wherein said β-secretase substrate molecule is selected from the group consisting of APPwt, APPsw, and β-secretase cleavable fragments thereof.

283. (New) The cell of claim 279, wherein said β-secretase substrate is selected from the group consisting of a maltose binding protein fused at the carboxy-terminus to the 125 carboxyl-terminal amino acids of APP having the cleavage site of SEQ ID NO: 54

(MBP-C125wt) and a maltose binding protein fused at the carboxy-terminus to the 125 C-terminus amino acids of APP having the cleavage site of SEQ ID NO: 51 (MBP-C125sw).

284. (New) The cell of claim 282, wherein said β-secretase-cleavable fragment is SEQ ID NO: 83.

285. (New) The cell of claim 282, wherein said β-secretase-cleavable fragment is SEQ ID NO: 84.

286. (New) The cell of claim 282, wherein said β-secretase-cleavable fragment is SEQ ID NO: 85.

287. (New) The cell of claim 282, wherein said β-secretase-cleavable fragment is SEQ ID NO: 86.

288. (New) The cell of claim 282, wherein said β-secretase-cleavable fragment is SEQ ID NO: 87.

289. (New) The cell of claim 282, wherein said β-secretase-cleavable fragment is SEQ ID NO: 88.

290. (New) The cell of claim 282, wherein said β-secretase-cleavable fragment is SEQ ID NO: 89.

291. (New) The cell of claim 282, wherein said β-secretase-cleavable fragment is SEQ ID NO: 90.

292. (New) The cell of claim 282, wherein said β-secretase-cleavable fragment is SEQ ID NO: 91.

293. (New) The cell of claim 282, wherein said β-secretase-cleavable fragment is SEQ ID NO: 92.

294. (New) The cell of claim 282, wherein said β-secretase-cleavable fragment is SEQ ID NO: 93.

295. (New) The cell of claim 282, wherein said β-secretase-cleavable fragment is SEQ ID NO: 94.

296. (New) The cell of claim 282, wherein said β-secretase-cleavable fragment is SEQ ID NO: 95.

297. (New) The cell of claim 282, wherein said β-secretase-cleavable fragment is SEQ ID NO: 96.

298. (New) A heterologous cell, comprising

(i) a nucleic acid molecule encoding SEQ ID NO: 67 or the complementary sequence of said nucleic acid molecule;

(ii) a nucleic acid molecule encoding a β-secretase substrate molecule; and

(iii) operatively linked to (i) and (ii), a regulatory sequence effective for expression of said nucleic acid molecules in said cell.

299. (New) The cell of claim 298, wherein said nucleic acid encoding said β-secretase protein is heterologous to said cell.

300. (New) The cell of claim 298, wherein both said nucleic acids encoding said β-secretase protein and encoding said β-secretase substrate molecule are heterologous to said cell.

301. (New) The cell of claim 298, wherein said β-secretase substrate molecule is selected from the group consisting of APPwt, APPsw, and β-secretase cleavable fragments thereof.

302. (New) The cell of claim 298, wherein said β-secretase substrate is selected from the group consisting of a maltose binding protein fused at the carboxy-terminus to the 125 carboxyl-terminal amino acids of APP having the cleavage site of SEQ ID NO: 54 (MBP-C125wt) and a maltose binding protein fused at the carboxy-terminus to the 125 C-terminus amino acids of APP having the cleavage site of SEQ ID NO: 51 (MBP-C125sw).

303. (New) The cell of claim 301, wherein said β-secretase-cleavable fragment is SEQ ID NO: 83.

304. (New) The cell of claim 301, wherein said β-secretase-cleavable fragment is SEQ ID NO: 84.

305. (New) The cell of claim 301, wherein said β-secretase-cleavable fragment is SEQ ID NO: 85.

306. (New) The cell of claim 301, wherein said β-secretase-cleavable fragment is SEQ ID NO: 86.

307. (New) The cell of claim 301, wherein said β-secretase-cleavable fragment is SEQ ID NO: 87.

308. (New) The cell of claim 301, wherein said β-secretase-cleavable fragment is SEQ ID NO: 88.

309. (New) The cell of claim 301, wherein said β-secretase-cleavable fragment is SEQ ID NO: 89.

310. (New) The cell of claim 301, wherein said β-secretase-cleavable fragment is SEQ ID NO: 90.

311. (New) The cell of claim 301, wherein said β-secretase-cleavable fragment is SEQ ID NO: 91.

312. (New) The cell of claim 301, wherein said β-secretase-cleavable fragment is SEQ ID NO: 92.

313. (New) The cell of claim 301, wherein said β-secretase-cleavable fragment is SEQ ID NO: 93.

312. (New) The cell of claim 301, wherein said β-secretase-cleavable fragment is SEQ ID NO: 94.

313. (New) The cell of claim 301, wherein said β-secretase-cleavable fragment is SEQ ID NO: 95.

314. (New) The cell of claim 301, wherein said β-secretase-cleavable fragment is SEQ ID NO: 96.

315. (New) A heterologous cell, comprising

(i) a nucleic acid molecule encoding SEQ ID NO: 68 or the complementary sequence of said nucleic acid molecule;

(ii) a nucleic acid molecule encoding a β-secretase substrate molecule; and

(iii) operatively linked to (i) and (ii), a regulatory sequence effective for expression of said nucleic acid molecules in said cell.

316. (New) The cell of claim 315, wherein said nucleic acid encoding said β-secretase protein is heterologous to said cell.

317. (New) The cell of claim 315, wherein both said nucleic acids encoding said β-secretase protein and encoding said β-secretase substrate molecule are heterologous to said cell.

318. (New) The cell of claim 315, wherein said β-secretase substrate molecule is selected from the group consisting of APPwt, APPsw, and β-secretase cleavable fragments thereof.

319. (New) The cell of claim 315, wherein said β-secretase substrate is selected from the group consisting of a maltose binding protein fused at the carboxy-terminus to the 125 carboxyl-terminal amino acids of APP having the cleavage site of SEQ ID NO: 54 (MBP-C125wt) and a maltose binding protein fused at the carboxy-terminus to the 125 C-terminus amino acids of APP having the cleavage site of SEQ ID NO: 51 (MBP-C125sw).

320. (New) The cell of claim 318, wherein said β-secretase-cleavable fragment is SEQ ID NO: 83.

321. (New) The cell of claim 318, wherein said β-secretase-cleavable fragment is SEQ ID NO: 84.

322. (New) The cell of claim 318, wherein said β-secretase-cleavable fragment is SEQ ID NO: 85.

323. (New) The cell of claim 318, wherein said β-secretase-cleavable fragment is SEQ ID NO: 86.

324. (New) The cell of claim 318, wherein said β-secretase-cleavable fragment is SEQ ID NO: 87.

325. (New) The cell of claim 318, wherein said β-secretase-cleavable fragment is SEQ ID NO: 88.

326. (New) The cell of claim 318, wherein said β-secretase-cleavable fragment is SEQ ID NO: 89.

327. (New) The cell of claim 318, wherein said β-secretase-cleavable fragment is SEQ ID NO: 90.

328. (New) The cell of claim 318, wherein said β-secretase-cleavable fragment is SEQ ID NO: 91.

329. (New) The cell of claim 318, wherein said β-secretase-cleavable fragment is SEQ ID NO: 92.

330. (New) The cell of claim 318, wherein said β-secretase-cleavable fragment is SEQ ID NO: 93.

331. (New) The cell of claim 318, wherein said β-secretase-cleavable fragment is SEQ ID NO: 94.

332. (New) The cell of claim 318, wherein said β-secretase-cleavable fragment is SEQ ID NO: 95.

333. (New) The cell of claim 318, wherein said β-secretase-cleavable fragment is SEQ ID NO: 96.

334. (New) A heterologous cell, comprising

(i) a nucleic acid molecule encoding SEQ ID NO: 69 or the complementary sequence of said nucleic acid molecule;

(ii) a nucleic acid molecule encoding a β-secretase substrate molecule; and

(iii) operatively linked to (i) and (ii), a regulatory sequence effective for expression of said nucleic acid molecules in said cell.

335. (New) The cell of claim 334, wherein said nucleic acid encoding said β-secretase protein is heterologous to said cell.

336. (New) The cell of claim 334, wherein both said nucleic acids encoding said β-secretase protein and encoding said β-secretase substrate molecule are heterologous to said cell.

337. (New) The cell of claim 334, wherein said β-secretase substrate molecule is selected from the group consisting of APPwt, APPsw, and β-secretase cleavable fragments thereof.

338. (New) The cell of claim 334, wherein said β-secretase substrate is selected from the group consisting of a maltose binding protein fused at the carboxy-terminus to the 125 carboxyl-terminal amino acids of APP having the cleavage site of SEQ ID NO: 54 (MBP-C125wt) and a maltose binding protein fused at the carboxy-terminus to the 125 C-terminus amino acids of APP having the cleavage site of SEQ ID NO: 51 (MBP-C125sw).

339. (New) The cell of claim 337, wherein said β-secretase-cleavable fragment is SEQ ID NO: 83.

340. (New) The cell of claim 337, wherein said β-secretase-cleavable fragment is SEQ ID NO: 84.

341. (New) The cell of claim 337, wherein said β-secretase-cleavable fragment is SEQ ID NO: 85.

342. (New) The cell of claim 337, wherein said β-secretase-cleavable fragment is SEQ ID NO: 86.

343. (New) The cell of claim 337, wherein said β-secretase-cleavable fragment is SEQ ID NO: 87.

344. (New) The cell of claim 337, wherein said β-secretase-cleavable fragment is SEQ ID NO: 88.

345. (New) The cell of claim 337, wherein said β-secretase-cleavable fragment is SEQ ID NO: 89.

346. (New) The cell of claim 337, wherein said β-secretase-cleavable fragment is SEQ ID NO: 90.

347. (New) The cell of claim 337, wherein said β-secretase-cleavable fragment is SEQ ID NO: 91.

348. (New) The cell of claim 337, wherein said β-secretase-cleavable fragment is SEQ ID NO: 92.

349. (New) The cell of claim 337, wherein said β-secretase-cleavable fragment is SEQ ID NO: 93.

350. (New) The cell of claim 337, wherein said β-secretase-cleavable fragment is SEQ ID NO: 94.

351. (New) The cell of claim 337, wherein said β-secretase-cleavable fragment is SEQ ID NO: 95.

352. (New) The cell of claim 337, wherein said β-secretase-cleavable fragment is SEQ ID NO: 96.

353. (New) A heterologous cell, comprising

(i) a nucleic acid molecule encoding SEQ ID NO: 70 or the complementary sequence of said nucleic acid molecule;

(ii) a nucleic acid molecule encoding a β-secretase substrate molecule; and

(iii) operatively linked to (i) and (ii), a regulatory sequence effective for expression of said nucleic acid molecules in said cell.

354. (New) The cell of claim 353, wherein said nucleic acid encoding said β-secretase protein is heterologous to said cell.

355. (New) The cell of claim 353, wherein both said nucleic acids encoding said β-secretase protein and encoding said β-secretase substrate molecule are heterologous to said cell.

356. (New) The cell of claim 353, wherein said β-secretase substrate molecule is selected from the group consisting of APPwt, APPsw, and β-secretase cleavable fragments thereof.

357. (New) The cell of claim 353, wherein said β-secretase substrate is selected from the group consisting of a maltose binding protein fused at the carboxy-terminus to the 125 carboxyl-terminal amino acids of APP having the cleavage site of SEQ ID NO: 54 (MBP-C125wt) and a maltose binding protein fused at the carboxy-terminus to the 125 C-terminus amino acids of APP having the cleavage site of SEQ ID NO: 51 (MBP-C125sw).

358. (New) The cell of claim 356, wherein said β-secretase-cleavable fragment is SEQ ID NO: 83.

359. (New) The cell of claim 356, wherein said β-secretase-cleavable fragment is SEQ ID NO: 84.

360. (New) The cell of claim 356, wherein said β-secretase-cleavable fragment is SEQ ID NO: 85.

361. (New) The cell of claim 356, wherein said β-secretase-cleavable fragment is SEQ ID NO: 86.

362. (New) The cell of claim 356, wherein said β-secretase-cleavable fragment is SEQ ID NO: 87.

363. (New) The cell of claim 356, wherein said β-secretase-cleavable fragment is SEQ ID NO: 88.

364. (New) The cell of claim 356, wherein said β-secretase-cleavable fragment is SEQ ID NO: 89.

365. (New) The cell of claim 356, wherein said β-secretase-cleavable fragment is SEQ ID NO: 90.

366. (New) The cell of claim 356, wherein said β-secretase-cleavable fragment is SEQ ID NO: 91.

367. (New) The cell of claim 356, wherein said β-secretase-cleavable fragment is SEQ ID NO: 92.

368. (New) The cell of claim 356, wherein said β-secretase-cleavable fragment is SEQ ID NO: 93.

369. (New) The cell of claim 356, wherein said β-secretase-cleavable fragment is SEQ ID NO: 94.

370. (New) The cell of claim 356, wherein said β-secretase-cleavable fragment is SEQ ID NO: 95.

371. (New) The cell of claim 356, wherein said β-secretase-cleavable fragment is SEQ ID NO: 96.

372. (New) A heterologous cell, comprising

(i) a nucleic acid molecule encoding SEQ ID NO: 74 or the complementary sequence of said nucleic acid molecule;

(ii) a nucleic acid molecule encoding a β-secretase substrate molecule; and

(iii) operatively linked to (i) and (ii), a regulatory sequence effective for expression of said nucleic acid molecules in said cell.

373. (New) The cell of claim 372, wherein said nucleic acid encoding said β-secretase protein is heterologous to said cell.

374. (New) The cell of claim 372, wherein both said nucleic acids encoding said β-secretase protein and encoding said β-secretase substrate molecule are heterologous to said cell.

375. (New) The cell of claim 372, wherein said β-secretase substrate molecule is selected from the group consisting of APPwt, APPsw, and β-secretase cleavable fragments thereof.

376. (New) The cell of claim 372, wherein said β-secretase substrate is selected from the group consisting of a maltose binding protein fused at the carboxy-terminus to the 125 carboxyl-terminal amino acids of APP having the cleavage site of SEQ ID NO: 54 (MBP-C125wt) and a maltose binding protein fused at the carboxy-terminus to the 125 C-terminus amino acids of APP having the cleavage site of SEQ ID NO: 51 (MBP-C125sw).

377. (New) The cell of claim 375, wherein said β-secretase-cleavable fragment is SEQ ID NO: 83.

378. (New) The cell of claim 375, wherein said β-secretase-cleavable fragment is SEQ ID NO: 84.

379. (New) The cell of claim 375, wherein said β-secretase-cleavable fragment is SEQ ID NO: 85.

380. (New) The cell of claim 375, wherein said β-secretase-cleavable fragment is SEQ ID NO: 86.

381. (New) The cell of claim 375, wherein said β-secretase-cleavable fragment is SEQ ID NO: 87.

382. (New) The cell of claim 375, wherein said β-secretase-cleavable fragment is SEQ ID NO: 88.

383. (New) The cell of claim 375, wherein said β-secretase-cleavable fragment is SEQ ID NO: 89.

384. (New) The cell of claim 375, wherein said β-secretase-cleavable fragment is SEQ ID NO: 90.

385. (New) The cell of claim 375, wherein said β-secretase-cleavable fragment is SEQ ID NO: 91.

386. (New) The cell of claim 375, wherein said β-secretase-cleavable fragment is SEQ ID NO: 92.

387. (New) The cell of claim 375, wherein said β-secretase-cleavable fragment is SEQ ID NO: 93.

388. (New) The cell of claim 375, wherein said β-secretase-cleavable fragment is SEQ ID NO: 94.

389. (New) The cell of claim 375, wherein said β-secretase-cleavable fragment is SEQ ID NO: 95.

390. (New) The cell of claim 375, wherein said β-secretase-cleavable fragment is SEQ ID NO: 96.

REMARKS/ARGUMENTS

After entry of this amendment, claims 48, 51-69, and 114-390 are pending and under consideration, claims 49-50 and 70-113 having been canceled and new claims 114-390 having been added. Claims 48, 51, 58, and 62 have been amended.

Independent claim 48 has been amended to delete "SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 69." New independent claims 131, 139, 155 are directed to SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 69, respectively. New dependent claims depending from independent claims 131, 139, 155 correspond to the claims depending from independent claim 48, *i.e.*, claims 51-57 correspond to claims 132-138, 140-146, and 156-162, respectively. Thus, new claims 131-146 and 155-162 contain no new matter.

New independent claims 114, 122, 147, 163, 171 correspond in part to claim 48. New independent claims 114, 122, 147, 163, 171, respectively, are directed to an isolated nucleic acid, comprising a sequence of nucleotides that encodes SEQ ID NOS: 58; 59; 68; 70; and 74 or a complementary sequence of any of such nucleotides have been added. Applicants note that the Examiner allowed claim 58, which is directed in part to a method of producing a recombinant beta-secretase, comprising culturing a cell transfected with a vector comprising a sequence of nucleotides that encodes SEQ ID NO: 58; SEQ ID NO 59; SEQ ID NO 68; SEQ ID NO 70; and SEQ ID NO 74. New dependent claims depending from independent claims 114, 122, 147, 163, 171 correspond in part to the claims depending from independent claim 48, *i.e.*, claims 51-57 correspond to claims 115-121, 123-130, 148-154, 164-170, and 172-178, respectively. Support for new claims 114, 122, 147, 163, 171 is provide at, *e.g.*, pages 7-8 of the specification. Support for new claim 114 is also provided by original claim 50. Thus, new claims 114-130, 147-154, and 163-178 contain no new matter.

Claim 51 has been amended to improve clarity. Support of the amendment is provided at , *e.g.*, page 40, lines 27-28.

Independent claim 58 is directed to a method of producing a recombinant β-secretase enzyme, comprising culturing a cell transfected with a vector comprising a sequence of nucleotides that encodes SEQ ID NO: 43. Claim 58 has been amended to delete "SEQ ID NO: 2;

SEQ ID NO: 56; SEQ ID NO: 57; SEQ ID NO: 58; SEQ ID NO: 59; SEQ ID NO: 60; SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 69; SEQ ID NO: 70; SEQ ID NO: 74; SEQ ID NO: 75." New independent claims 179, 185, 197, 203, 209, 215, and 221 are directed to a method of producing a recombinant β-secretase enzyme, comprising culturing a cell transfected with a vector comprising a sequence of nucleotides that encodes SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 67; SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, and SEQ ID NO: 74, respectively. New dependent claims depending from independent claims 179, 185, 197, 203, 209, 215, and 221 correspond to the claims depending from independent claim 58, *i.e.*, claims 59-63 correspond to claims 180-184, 186-190 192-196, 198-202, 204-208, 210-214, 216-220, 222-226, respectively. Thus, new claims 179-226 contain no new matter.

Independent claim 64 is directed to a heterologous cell, comprising (i) a nucleic acid molecule encoding SEQ ID NO: 43 or the complementary sequence of said nucleic acid molecule; (ii) a nucleic acid molecule encoding a β-secretase substrate molecule; and (iii) operatively linked to (i) and (ii), a regulatory sequence effective for expression of said nucleic acid molecules in said cell. Claim 64 has been amended to delete "SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 69." New independent claims 279, 298, 334 are directed to SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 69, respectively. New dependent claims, which respectively depend from independent claims 279, 298, 334, correspond to the claims depending from independent claim 64, *i.e.*, claims 65-69 (as discussed below, claim 69 has been represented as new claims 227-240) correspond to claims 280-297, 299-314, and 335-353, respectively. Thus, new claims 279-314 and 335-353 contain no new matter.

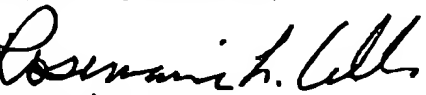
Claim 69, which depends from claim 67, recites, "wherein the β-secretase cleavable fragment is SEQ ID NO: 82. Claim 69 has been amended to delete "SEQ ID NO: 83; SEQ ID NO: 84; SEQ ID NO: 85; SEQ ID NO: 86; SEQ ID NO: 87; SEQ ID NO: 88; SEQ ID NO: 89; SEQ ID NO: 90; SEQ ID NO: 91; SEQ ID NO: 92; SEQ ID NO: 93; SEQ ID NO: 94; SEQ ID NO: 95; and SEQ ID NO: 96." New dependent claims 227-240 are directed to β-secretase cleavable fragments of SEQ ID NO: 83, SEQ ID NO: 84, SEQ ID NO: 85, SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 91,

SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94, SEQ ID NO: 95, and SEQ ID NO: 96 respectively.

New independent claims 241, 260, 315, 353, and 372 correspond in part to claim 64. New independent claims 241, 260, 315, 353, 372, respectively, are directed to an isolated nucleic acid, comprising a sequence of nucleotides that encodes SEQ ID NOS: 58; 59; 68; 70; and 74 or a complementary sequence of any of such nucleotides have been added. Applicants note that the Examiner allowed claim 58, which is directed in part to a method of producing a recombinant beta-secretase, comprising culturing a cell transfected with a vector comprising a sequence of nucleotides that encodes SEQ ID NO: 58; SEQ ID NO 59; SEQ ID NO 68; SEQ ID NO 70; and SEQ ID NO 74. Support for new claims 241, 260, 315, 353, and 372 is provide at, *e.g.*, page 38, lines 25-28 and page 40, lines 11-16 of the specification. Thus, new claims 241, 260, 315, 353, and 372 contain no new matter. New dependent claims, which respectively depend from independent claims 241, 260, 315, 353, 372, correspond to the claims depending from independent claim 64, *i.e.*, claims 65-69 (as discussed above, claim 69 has been represented as new claims 227-240) correspond to new dependent claims 242-259, 261-278, 316-333, 354-371, 373-390.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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PTO/SB/30 (09-04)

Request for Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	09/471,669
Filing Date	December 24, 1999
First Named Inventor	Anderson, John P.
Art Unit	1652
Examiner Name	Walicka, Malgorzata A.
Attorney Docket Number	015270-006430US

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

   a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

      i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

      ii. ☐ Other _____

   b. ☒ Enclosed

      i. ☒ Amendment/Reply (34 pages)

      ii. ☐ Affidavit(s)/ Declaration(s)

      iii ☒ Information Disclosure Statement (IDS) (2 pages); PTO/SB/08A (1 page); copies of cited ref. 113-138;

      iv. ☒ Other Fee Transmittal (1 pg., submitted in dupl.) Petition to Withdraw Application From Issuance (2 pgs)

2. Miscellaneous

   a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

   b. ☐ Other _____

3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

   a. ☒ The Director is hereby authorized to charge the following fees, or credit any overpayments, to Deposit Account No. 20-1430. I have enclosed a duplicate copy of this sheet.

      i. ☒ RCE fee required under 37 CFR 1.17(e)

      ii. ☐ Extension of time fee (37 CFR 1.136 and 1.17)

      iii. ☐ Other _____

   b. ☐ Check in the amount of $ _____ enclosed

   c. ☐ Payment by credit card (Form PTO-2038 enclosed)

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization of PTO-2038.

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SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	Rosemarie L. Celli	Date	November 22, 2004
Name (Print/Type)	Rosemarie L. Celli	Registration No.	42,397

CERTIFICATE OF MAILING OR TRANSMISSION

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I hereby certify that this correspondence is being deposited with the United States Postal Service with "Express Mail Post Office to Address" service under 37 CFR 1.10 on this date November 22, 2004 and is addressed to: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Signature	Jordan Maglet		
Name (Print/Type)	Jordan Maglet	Date	11/22/04

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To:	**At Fax Number:**	**Confirmation Phone Number:**
Sherry Brinkley **USPTO - Office of Petitions**	**571-273-0025**	**571-272-3204**

From: Steven C. Garland **(3816)**

Message: Dear Ms. Brinkley,

Pursuant to our telephone conversation this morning, I am forwarding copies of the following papers which were filed via Express Mail on November 22, 2004 regarding Application No. 09/471,669:

1. Request for Continued Examination (RCE) Transmittal (1 page);
2. Fee Transmittal (PTO/SB/17(1 page, submitted in duplicate);
3. Amendment (34 pages);
4. Supplemental Information Disclosure Statement (2 pages);
5. PTO/SB/08A (1 page);
6. Petition to Withdraw Application From Issuance Pursuant to 37 CFR §1.313(c)(2) (2 pgs); and
7. Return postcard.

Also attached is a copy of Express Mail No. EV 530 886 675 US bearing the USPS' "date in" stamp of November 22, 2004.

Because an Issue Notification was mailed subsequent to the above filing, your prompt attention to this matter will be greatly appreciated.

- Steve Garland

Original Will:		BE SENT BY MAIL		BE SENT BY FEDEX/OVERNIGHT COURIER		BE SENT BY MESSENGER	X	NOT BE SENT

Faxed: Return to: Steven C. Garland - (5279)

If you have problems with reception please call Fax Services at extension **5565**

PTO/SB/17 (10-04)

FEE TRANSMITTAL for FY 2005

Effective 10/01/2004. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 3748

Complete if Known	
Application Number	09/471,669
Filing Date	December 24, 1999
First Named Inventor	Anderson, John P.
Examiner Name	Walicka, Malgorzata A.
Art Unit	1652
Attorney Docket No.	015270-006430US

COPY

FAX RECEIVED DEC 06 2004

OFFICE OF PETITIONS

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit Card ☐ Money Order ☐ Other ☐ None

☒ Deposit Account:

Deposit Account Number: 20-1430

Deposit Account Name: Townsend and Townsend and Crew LLP

The Director is authorized to: *(check all that apply)*

☒ Charge fee(s) indicated below ☒ Credit any overpayments

☒ Charge any additional fee(s) or any underpayment of fee(s)

☐ Charge fee(s) indicated below, except for the filing fee to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	790	2001	395	Utility filing fee	
1002	350	2002	175	Design filing fee	
1003	550	2003	275	Plant filing fee	
1004	790	2004	395	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($)

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

			Extra Claims	Fee from below	Fee Paid
Total Claims	390	-316** =	74	x18 =	1332
Independent Claims	23	-8 =	17	x88 =	1496
Multiple Dependent				x =	

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	88	2201	44	Independent claims in excess of 3
1203	300	2203	150	Multiple dependent claim, if not paid
1204	88	2204	44	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)2828

**or number previously paid, if greater; For Reissues, see above

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	430	2252	215	Extension for reply within second month	
1253	980	2253	490	Extension for reply within third month	
1254	1,530	2254	765	Extension for reply within fourth month	
1255	2,080	2255	1,040	Extension for reply within fifth month	
1401	340	2401	170	Notice of Appeal	
1402	340	2402	170	Filing a brief in support of an appeal	
1403	300	2403	150	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive – unavoidable	
1453	1,330	2453	665	Petition to revive – unintentional	
1501	1,370	2501	685	Utility issue fee (or reissue)	
1502	490	2502	245	Design issue fee	
1503	660	2503	330	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	130
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	790	2809	395	Filing a submission after final rejection (37 CFR § 1.129(a))	
1810	790	2810	395	For each additional invention to be examined (37 CFR § 1.129(b))	
1801	790	2801	395	Request for Continued Examination (RCE)	790
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify)

*Reduced by Basic Filing Fee Paid SUBTOTAL (3) ($)920

SUBMITTED BY				Complete (if applicable)	
Name (Print/Type)	Rosemarie L. Celli	Registration No. (Attorney/Agent)	42,397	Telephone	650-326-2400
Signature	Rosemarie L. Celli			Date	November 22, 2004

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

60359453 v1

"Express Mail" Label No. EV 530 886 675 US
Date of Deposit November 22, 2004

I hereby certify that this is being deposited with the United States Postal Service "Express Mail Post Office to Address" service under 37 CFR 1.10 on the date indicated above and is addressed to:

Mail Stop Petitions
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

By: _____

PATENT
Attorney Docket No.: 015270-006430US
Client Reference No.: 228-US-NEW

#46

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

John P. Anderson et al.

Application No.: 09/471,669

Filed: December 24, 1999

For: BETA-SECRETASE ENZYME COMPOSITIONS AND METHODS

Examiner: Walicka, Malgorzata A.

Art Unit: 1652

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.97 and §1.98

Mail Stop Petitions
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The references cited on attached form PTO/SB/08A are being called to the attention of the Examiner. Copies of the citation nos. 113-138 are enclosed. It is respectfully requested that the cited references be expressly considered during the prosecution of this application, and the references be made of record therein and appear among the "references cited" on any patent to issue therefrom.

PATENT

As provided for by 37 CFR 1.97(g) and (h), no representation is being made that a search has been conducted or that this statement encompasses all the possible relevant information, and no inference should be made that the information and references cited are, or are considered to be material to patentability because they are in this statement. No inference should be made that the information and references cited are prior art merely because they are in this statement.

Applicant believes that no fee is required for submission of this statement. This paper is being submitted with an RCE. However, if a fee is required, the Commissioner is authorized to deduct such fee from the undersigned's Deposit Account No. 20-1430. Please deduct any additional fees from, or credit any overpayment to, the above-noted Deposit Account.

Respectfully submitted,

Rosemarie L. Celli
Reg. No. 42,397

TOWNSEND and TOWNSEND and CREW LLP
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Tel: 650-326-2400
Fax: 650-326-2422
RLC:scg
60360410 v1

PTO-SB-08A (06-03)

Substitute for form 1449A-PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet | 1 | of | 1

Complete if Known	
Application Number	09/471,669
Filing Date	December 24, 1999
First Named Inventor	Anderson, John P., et. al.
Art Unit	1652
Examiner Name	Walicka, Malgorzata A.
Attorney Docket Number	015270-006430US

U.S. PATENT DOCUMENTS

Examiner	Cite No.[1]	Document Number: Number Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	113	US 6,797,487 B2	09-28-2004	Gurney et al.	
	114	US 6,790,610 B2	09-14-2004	Gurney et al.	
	115	US 6,753,163 B2	06-22-2004	Gurney et al.	
	116	US 6,737,510 B1	05-18-2004	Gurney et al.	
	117	US 6,727,074 B2	04-27-2004	Gurney et al.	
	118	US 6,706,485 B1	03-16-2004	Gurney et al.	
	119	US 6,699,671 B1	03-02-2004	Gurney et al.	
	120	US 6,500,667 B1	12-31-2002	Gurney et al.	
	121	US 6,440,698 B1	08-27-2002	Gurney et al.	
	122	US 6,420,534 B1	07-16-2002	Gurney et al.	
	123	US 2004/0166507 A1	08-26-2004	Gurney et al.	
	124	US 2004/0048303 A1	03-11-2004	Gurney et al.	
	125	US 2004/0043408 A1	03-04-2004	Gurney et al.	
	126	US 2003/0104365 A1	06-05-2003	Gurney et al.	
	127	US 2003/0077226 A1	04-24-2003	Gurney et al.	
	128	US 2002/0081634 A1	06-27-2002	Gurney et al.	
	129	US 2002/0064819 A1	05-30-2002	Gurney et al.	
	130	US 2002/0037315 A1	03-28-2002	Gurney et al.	
	131	US 2001/0021391 A1	09-13-2001	Gurney et al.	
	132	US 2001/0018208 A1	08-30-2001	Gurney et al.	
	133	US 2001/0016324 A1	08-23-2001	Gurney et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document: Country Code[3]	Number[4]	Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	134	WO	01/50829	A2	07-19-2001	Bienkowski et al.		☐
	135	WO	01/49098	A2	07-12-2001	Bienkowski et al.		☐
	136	WO	01/49097	A2	07-12-2001	Bienkowski et al.		☐
	137	WO	01/23533	A2	04-05-2001	Gurney et al.		☐
	138	WO	00/17369	A2	03-30-2000	Gurney et al.		☐

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.